CH 500 661

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MAIN PATENT
CIBA-GEIGY AG, Basel

THE USE OF SALICYLIC ACID O-HYDROXYPHENYLAMIDES TO CONTROL HARMFUL MICROORGANISMS OUTSIDE OF THE TEXTILE INDUSTRY

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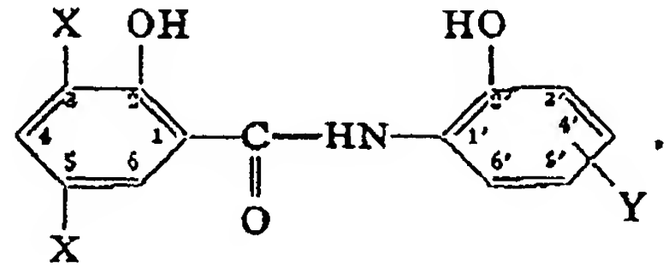
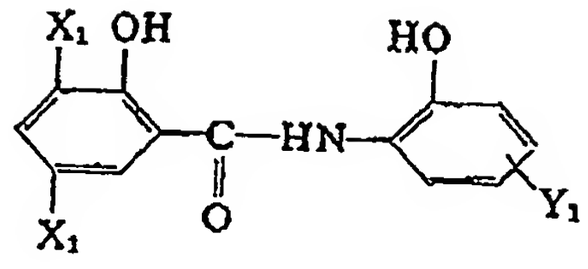
Description

The object of the invention is the use of salicylic acid o-hydroxyphenylamides of the formula

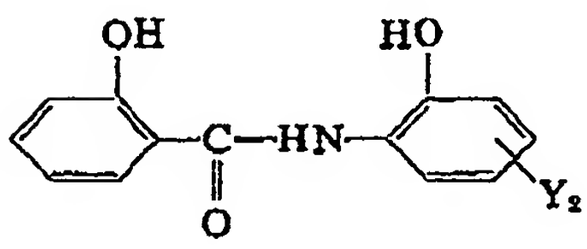
(1) 

in which X is a hydrogen atom or halogen atom and Y is a trifluoromethyl group, an alkyl group with a maximum of 12 carbon atoms, a cycloalkyl residue, a phenyl residue or a aralkyl residue, where an alkyl group Y contains at least 8 carbon atoms if X stands for hydrogen, to combat harmful microorganisms outside of the textile industry.

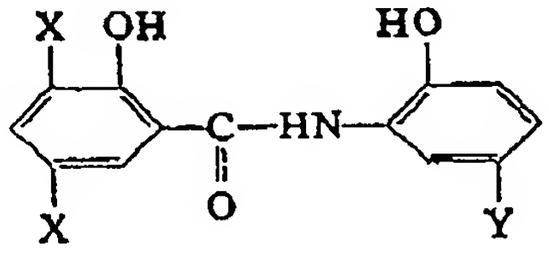
These salicylic acid o-hydroxyphenylamides of formula (1) (hereinafter also in some cases simply called salicylic acid amides) thus correspond to the one of the formulas

(2) 

and

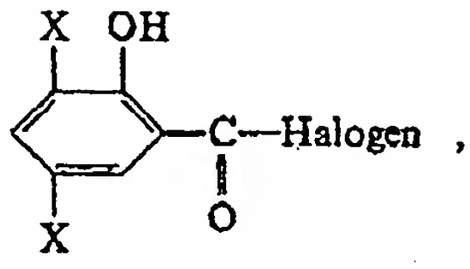
(3) 

here X_1 means a halogen atom, preferably a chlorine or bromine atom, Y_1 means a trifluoromethyl group, an alkyl group with a maximum of 12 carbon atoms, a cycloalkyl residue, a phenyl residue or an arylalkyl residue, and Y_2 means a trifluoromethyl group, an alkyl group with 8 to 12 carbon atoms, a cycloalkyl residue, a phenyl residue or an aralkyl residue. The substituent Y, or Y_1, or Y_2, is, for example, in p position to the HN group and preferably in p position to the HO group:

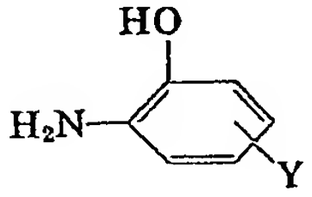
(4) 

If Y is an alkyl group, it can be unbranched or branched. Examples that may be mentioned include n-octyl, n-dodecyl and 1,1,3,3-tetramethylbutyl groups, and the salicylic acid residue contains two halogen atoms, methyl, ethyl, n-propyl, isopropyl and tert-butyl groups may be mentioned. Possibilities as cycloalkyl residues are first of all cyclohexyl residues and as aralkyl residue possibilities are, for example, benzyl residues or especially 1,1-dimethyl-1-phenylmethyl residues (cumyl residues).

The salicylic acid amides of formula (1) can expediently be produced through condensation of salicylic acid halides of the formula

(5) 

especially salicylic acid chloride or the chlorides of 3,5-dibromo- or 3,5-dichlorosalicylic acid, with o-hydroxylaminobenzenes of the formula

(6) 

where X and Y have the meanings given above. One preferably operates in an inert organic solvent and with the addition of an acid-forming agent, for example an aqueous sodium hydroxide solution.

Agents for combating harmful microorganisms can be made with the salicylic acid amides of formulas (1) to (3) and can be used in conventional substantially known ways. The broad antibacterial spectrum of action, which extends both to gram-positive and to gram-negative bacteria, is especially valuable with the new agents. Here the odorlessness and colorlessness of the salicylic acid amides is of particular value from the standpoint of application technology. This invention thus also includes their use in pest control quite generally. Their use is possible on a very broad basis, especially for protection of organic substrates outside the textile industry against attack by destructive and pathogenic (also phytopathogenic) microorganisms. The new salicylic acid amides are accordingly suitable both as preservatives and as disinfection agents for industrial products of all kinds, in plant protection, in agriculture.

The following may be mentioned as examples of the industrial products that can be preserved with the aid of the salicylic acid amides:

Sizing agents, binders, paints, coloring and printing pastes and similar preparations based on organic and inorganic dyes or pigments, also ones that contain casein or other organic compounds as components. Also, wall paints and finish paints, for example ones that contain a protein-containing color binder, are protected against attack by pests through the addition of the new compounds. The use for protection of wood is likewise possible.

The new salicylic acid amides can also be used in the pulp and paper industry as preservatives, among other things to prevent the well known formation of slime caused by microorganisms in equipment used for papermaking.

In addition, one can produce detergents and cleaning agents with excellent antibacterial or antimycotic action by combining the compounds of formulas (1) to (3) with substances that have detergent or surfactant activity. The salicylic acid amides can be incorporated, for example, into soaps, combined with soap-free, detergent-active or surface-active substances or with mixtures of soaps and soap-free detergent substances, and their antimicrobial efficacy is fully retained in these combinations.

Cleaning agents that contain a compound of formula (1) can be used in industry and at home, likewise in food businesses, for example dairies, breweries, and slaughterhouses. The salicylic acid amides can also be used as a component of preparations that serve the purposes of cleaning or disinfection in hospitals and in medical practice.

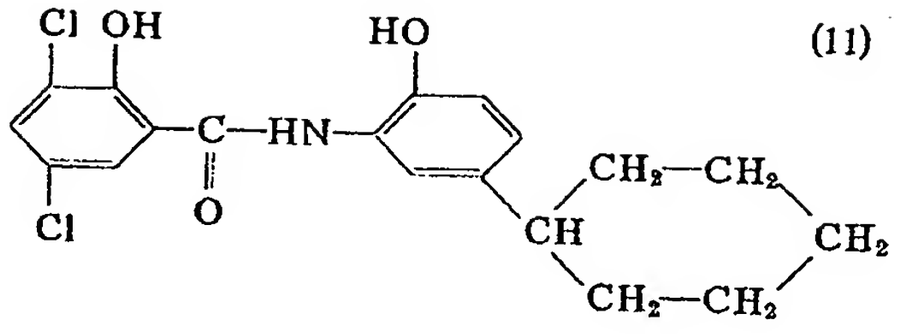
The effect can also be employed in preservative and disinfectant finishes for plastics such as polyvinyl chloride. When plasticizers are used, it is advantageous to add the salicylic acid amides to the plastic dissolved or dispersed in the plasticizer. It is expedient to see that the distribution in the plastic is as uniform as possible. Plastics with antimicrobial properties can find use for consumer objects of all kinds in which efficacy against various germs such as bacteria and fungi is desirable, for example in doormats, shower curtains, seats, gratings in swimming pools, wall coverings. By adding them to wax and polish compounds one obtains floor and furniture care agents with disinfectant action.

The forms for use can correspond to the conventional formulations of pest control agents, for example agents that contain a compound of formula (1) can optionally also contain additives such as carriers, solvents, diluents, dispersion agents, wetting agents or adhesion agents, as well as other pest control agents. Finally, more than one compound of formulas (1) through (3) can be present simultaneously in such agents for combating harmful microorganisms.

The parts indicated in the following examples are parts by weight and the percentages are percents by weight, unless otherwise specified.

Manufacturing procedures

22.6 parts 3,5-dichlorosalicylic acid chloride is dissolved in 100 parts by volume acetone. The solution is cooled to 5°C and at this temperature a solution of 19.1 parts 2-amino-4-cyclohexylphenol in a mixture of 100 parts by volume acetone and 100 parts by volume dioxane is added. The reaction mixture is mixed dropwise with 50 parts by volume 2N sodium hydroxide at 5-10°C for 10 minutes and then all of the reaction mixture is poured into ice water. The compound of the formula

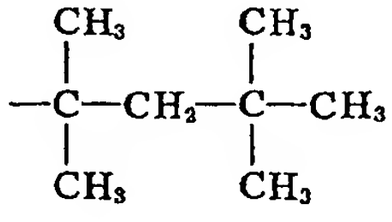
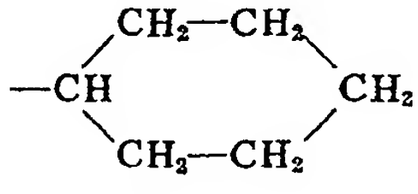
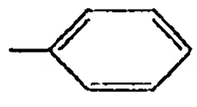
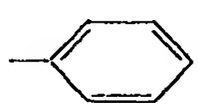
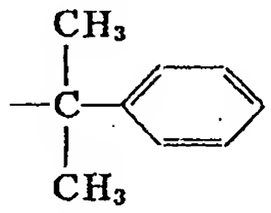
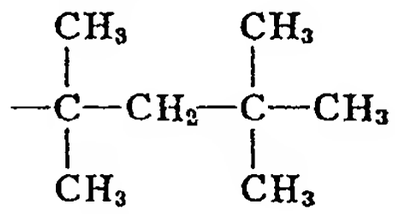
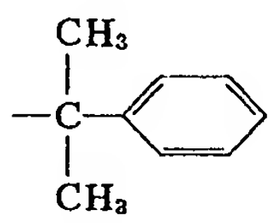
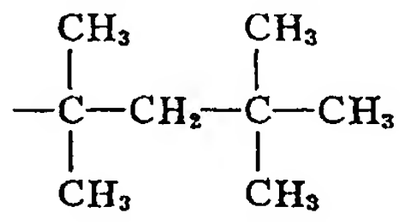
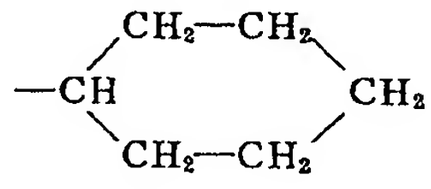
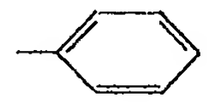


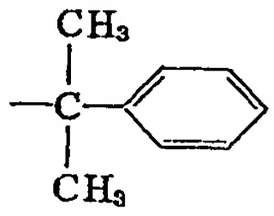
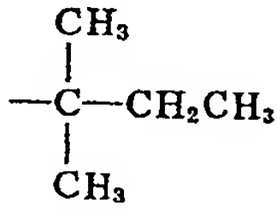
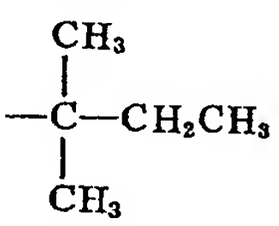
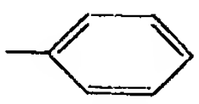
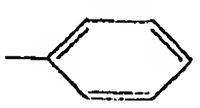
(11)

precipitates first as a viscous oil, but it then solidifies after a little stirring to form a crystalline mass and is then filtered out, washed with water and dried. The yield is roughly 34 parts; melting point 187-191°C.

After recrystallization from chlorobenzene roughly 23 parts of the pure compound, which melts at 198.5-199.5°C precipitates out.

The compounds of formula (1) listed in the following table, where X and Y have the meanings given, can be produced similarly.

Nr.	X	(1) Y (Stellung)		(2) Schmelzpunkt in °C
12	H		(5′)	155 bis 156
13	H		(5′)	145 bis 146
14	H		(4′)	203 bis 204
15	H		(5′)	188 bis 189
16	H		(5′)	122,5 bis 123,5
17	H	—CF_3	(5′)	191 bis 192
18	Cl	—CH_3	(4′)	194 bis 195
19	Cl	—CH_3	(5′)	193 bis 194
20	Cl	—$C(CH_3)_3$	(5′)	173 bis 175
21	Cl		(5′)	191,5 bis 192,5
22	Cl		(5′)	201 bis 202
23	Cl		(5′)	171,5 bis 172,5
24	Cl	—CF_3	(5′)	209 bis 210
25	Br	—CH_3	(4′)	196 bis 197
26	Br	—CH_3	(5′)	220 bis 221
27	Br	—$C(CH_3)_3$	(5′)	183 bis 184
28	Br		(5′)	172 bis 173
29	Br		(5′)	205 bis 206
30	Br		(5′)	204 bis 205

Nr.	X	Y (Stellung) (1)		(2) Schmelzpunkt in °C
31	Br		(5')	(3) 164 bis 165
32	Br	—CF_3	(5')	212 bis 213
33	Cl		(5')	158,5 bis 159,5
34	Br		(5')	170 bis 171
35	Cl	—CH_3	(3')	191 bis 191,5
36	Cl		(4')	218 bis 219
37	Br		(4')	235 bis 236
38	Cl	—$(CH_2)_{11}$—CH_3	(5')	115,5 bis 116,5

Key: 1 Y (position)
2 Melting point in °C
3 To

Determination of the minimal inhibitory concentration (MIC) for bacteria and fungi in a dilution test.

The determination of the MIC (minimal inhibitory concentration) takes place by testing in the teaching of standard norms that allows an approximation of absolute minimum inhibiting values of an active agent.

A 1% and a 0.3% solution of the active agents in dimethylsulfoxide are added to test tubes containing sterile brain heart infusion broth (bacteria) or beer wort solution (fungi) dilution tests are carried out with progressive tenfold dilution are carried out with the solutions. By combining the two series one obtains the following continuous dilution series:

1000, 300, 100, 30, 10, 3 ppm tc

The solutions are inoculated with the bacterium *Staphylococcus aureus* or with the fungi *Aspergillus niger* and *Rhizopus nigricans*. Then the mixtures are incubated for 48 hours at 37°C in the case of *Staphylococcus aureus* (bacteriostasis) and 72 hours at 30°C in the case of the fungi (fungistasis).

After the said times the minimal inhibitory values (ppm) in the following table are found.

Verbindung Nr. (1)	(2) Hemmwerte (ppm) der Bakteriostase (4) Staphylococcus aureus (3)	Fungistase (4) Aspergillus niger	Rhizopus nigricans
11	0,3	–	<100
12	1	–	–
13	1	–	–
14	3	–	–
15	10	–	–
16	3	–	–
17	100	100	30
18	10	–	<100
19	3	–	–
20	1	100	< 3
21	0,3	–	–
22	1	–	<100
23	0,3	–	<100
24	10	30	30
25	10	100	< 3
26	10	–	<100
27	3	–	–
28	0,3	–	<100
29	0,3	–	<100
30	1	–	<100
31	0,3	–	<100
32	10	–	<100
33	100	–	<100
34	1	–	<100
35	100	–	<100
36	1	–	–
37	1	–	–

Key:
1 Compound No.
2 Inhibitory value (ppm)
3 Bacteriostasis
4 Fungistasis

Determination of the minimal inhibitory concentration (MIC) for bacteria and fungi in the gradient plate test.

The compounds of formula (1) are mixed in suitable formulations (for example as solutions in dimethylsulfoxide) of specific concentration with warm brain heart infusion agar (bacteria) or mycophil agar (fungi). The liquid mixtures are poured onto a solidified wedge shaped base agar layer and likewise allowed to solidify.

The test organisms are now placed perpendicular to the gradients with a Pasteur pipette. After incubation for 24 hours at 37°C (bacteria) or 72 hours at 30°C (fungi) the length of the germs grown on the inoculation line is measured and expressed in ppm active agent.

	(2) minimale Hemmkonzentration (ppm)		
Verbindung Nr. (1)	Streptococcus mitis	Trichophyton interdigitale	Trichophyton mentagraphytes
11	0,5	1	2
12	2	10	1
13	30	0,3	0,3
19	1	10	10
20	10	1	3
21	0,2	2	2,5
22	2	3	3
25	40	2	2,5
27	0,4	2	4
28	0,4	2	3
29	0,5	2	2
30	0,9	2	3
31	0,1	2	4
37	0,5	2	2,5

Key: 1 Compound No.
2 Minimal inhibitory concentration (ppm)

Example 1

To produce an antimicrobial hard soap 1.2 g of the compound of formula (28) is added to the following mixture:

120 g base soap in flake form

0.12 g disodium salt of ethylene diamine tetraacetic acid (dihydrate)

0.24 g titanium dioxide

The soap chips obtained by rolling are pulverized with a high speed stirrer and then pressed into soap pieces.

A 5% and a 1.5% solution are prepared in sterile tap water with antimicrobial soap. 1 mL of each of these solutions is added to 4 mL sterile brain heart infusion broth. By progressive tenfold dilution in each case two series are obtained, which results in the following dilution series through combination:

100, 30, 10, 3, 1 . . . ppm active agent.

The solutions are inoculated with the bacteria *Staphylococcus aureus* or *Escherichia coli* and incubated for 24 hours at 37°C. After this time 0.05 mL of these solutions is taken up with a pipette and it is allowed to flow over a brain heart infusion agar slant. Solutions (bacteriostasis) and agar tubes (bactericides) are then incubated for another 24 hours at 37°C.

The minimal inhibitory or eradication concentration (ppm) is now determined for the solutions and the agar slant tubes:

	(1) Wirkung gegenüber Staphylococcus aureus	Escherichia coli
(2) Bakteriostase (48 Stunden)	<0,1 ppm	100
Bakterizidie (24 Stunden)	<0,1 ppm	100

Key: 1 Effect against
2 Bacteriostasis (48 h)
3 Bactericide (24 h)

Example 2

The following mixture is rolled for 20 minutes at 150°C on a twin roll table:

100.00 parts polyvinyl chloride
45.25 parts di-2-ethylhexylphthalate
1.5 parts barium/cadmium laurate
0.25 parts stearic acid
7.75 parts of a solution of 1.55 parts of the compound of formula (37) in 6.25 parts di-2-ethylhexylphthalate.

The roller spacing is set so that 1 mm thick sheets result, which are then pressed at 14.00 kg/cm^2 for 80 minutes at 165 to 170°C.

To test the effect against bacteria, rondelles 10 mm in diameter are stamped from the soft polyvinyl chloride and placed on brain heart infusion agar plates that have been inoculated beforehand with *Staphylococcus aureus*. The plates are then incubated for 24 hours at 37°C.

The inhibitory zone (IZ in mm) arising around the rondelles on the one hand and the microscopically detectable growth (W in %) under or on the soft polyvinyl chloride on the other are now determined:

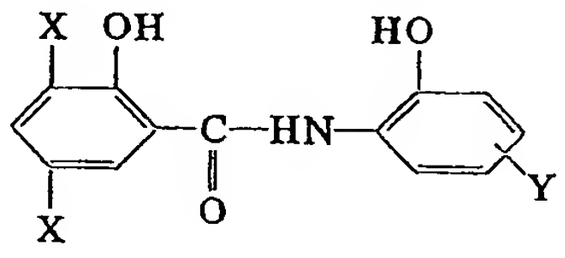
ungewässert		gewässert *	
HZ in mm	W in %	HZ in mm	W in %
3	0	3	0

* Wässerung: 24 Stunden bei 30° C.

Key:
1 IZ in mm
2 Not rinsed
3 Rinsed *
4 rinsing 24 h at 30°C

Claim

The use of salicylic acid o-hydroxyphenylamides of the formula



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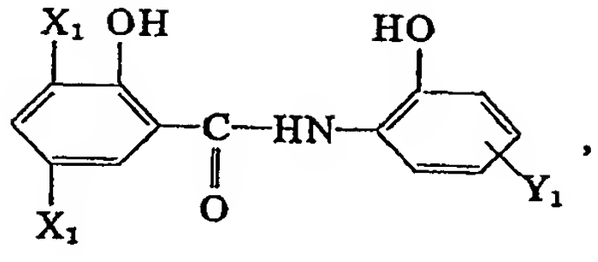
in which X means a hydrogen atom or a halogen atom and Y means a trifluoromethyl group, an alkyl group with a maximum of 12 carbon atoms, a cycloalkyl residue, a phenyl residue or aralkyl residue, where an alkyl group Y contains at least 8 carbon atoms if X stands for hydrogen, to combat harmful microorganisms outside of the textile industry.

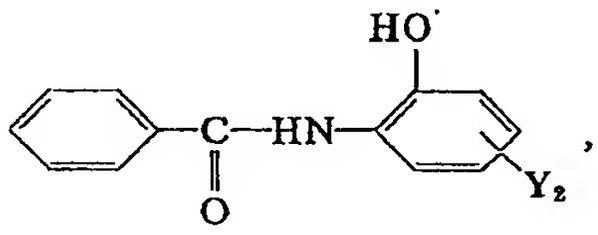
Secondary Claims

1. The use of salicylic acid o-hydroxyphenylamides



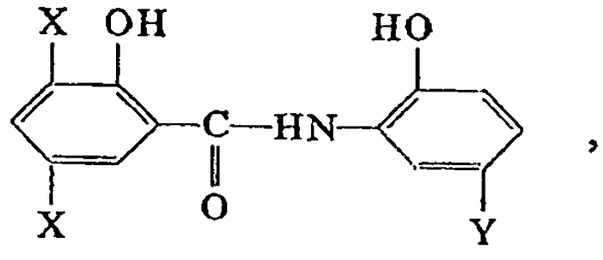
in which X_1 means a halogen atom and Y_1 means a trifluoromethyl group, an alkyl group with a maximum of 12 carbon atoms, a cycloalkyl residue, a phenyl residue or an aralkyl residue, in accordance with the main claim.

2. The use of salicylic acid o-hydroxyphenylamides of the formula



in which Y_2 means a trifluoromethyl group, an alkyl group with 8 to 12 carbon atoms, a cycloalkyl residue, a phenyl residue or an aralkyl residue, as in the main claim.

3. The use of salicylic acid o-hydroxyphenylamides of the formula



in which X and Y have the meanings given in the main claim, in accordance with the main claim.

4. The use of salicylic acid o-hydroxyphenylamides as in the main claim, subclaims 1 or 3, which contain two chlorine or bromine atoms in the salicylic acid residue in accordance with the main claim.

CIBA-GEIGY AG

Note of the Federal Department for Intellectual Property:

If parts of the description are not in correspondence with the definition of the invention given in the main claim, one should remember that in accordance with Art. 51 of the Patent Law the main claim is definitive for the actual area of validity of the patent.